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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,557	05/02/2002	Audrey Goddard	GNE.3230R1C39	9770

20995 7590 06/28/2006

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,557	GODDARD ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/11/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 April 2006 has been entered.

2. Claim 6 is canceled.

3. Claims 1-5 are pending and under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. This Office Action contains New Grounds of Objection.

Withdrawn Rejections

6. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, (separate from the utility rejection) because the claims contain subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn in view that this rejection duplicates the rejection of claims 1-5 for lack of enablement since the claimed invention is not supported by a substantial utility or a well-established utility (see item no. 7 below).

Response to Arguments

7. The rejection of claims 1-5 under 35 U.S.C 101 because the claimed invention is not supported by a substantial asserted utility or a well-established utility is maintained.

Applicant again summarizes the examiners position, the disputed issues, cites case law and MPEP. Applicant maintains that the asserted patentable utility of the PRO1069 polypeptide is based on the disclosure in Example 18 of the instant application that the mRNA encoding the PRO1069 polypeptide is "more highly expressed" in normal kidney tissue compared to kidney tumor tissue.

Beginning at page 7 of the response, Applicant argues the differential expression of PRO1069 mRNA was detected using the technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissues samples. Applicant argues that identification of the differential expression of the PRO1069 polypeptide-encoding gene in tumor tissues as compared to the corresponding normal tissue "renders the molecule useful diagnostic tool for the determination of the presence or absence of tumor." (pg 7). It is further asserted that because it is well established that changes in mRNA levels lead to changes in the level of the encoded protein, one would expect the PRO1069 protein to be differentially expressed in normal kidney compared to kidney tumor.

Applicant's arguments have been fully considered but are not found persuasive for the following reasons. An assay using PCR amplification as described in Example 18, the applicants merely measure the mRNA level; it does not measure the over-expression of the polypeptide of SEQ ID NO:50. There is no evidence regarding

whether the level of PRO1069 polypeptide of SEQ ID NO:50 is more highly expressed in normal kidney compared to kidney tumor. The specification does not disclose a correlation between any specific disorder and the altered level or form of the claimed PRO1069 polypeptide of SEQ ID NO:50, nor does it establish that the expression of PRO1069 is specific to kidney tumor. Thus, there is insufficient information or experimental data presented on whether the polypeptide or the antibodies binding such of the present invention can serve as a reliable diagnostic marker for distinguishing normal kidney from kidney tumor. Moreover, the assay does not establish a causative link between the polypeptide (or antibodies) of the present invention and kidney tumor. Without such critical information, one skilled in the art would not be able to use the polypeptide of the present invention as a therapeutic target for treatment of kidney tumor without further experimentation. The information disclosed in the instant specification is preliminary at best as there is no evidence or data that a change (i.e., decrease) in PRO1069 mRNA or polypeptide expression is tumor-dependent, consistent and measurable. Finally, the art indicates that the changes in mRNA expression do not correlate with polypeptide levels (e.g., Alberts [a], Alberts [b], Lewin, Zhigang, Meric, Greenbaum, Jang, Haynes et al, Gygi et al, Hanash [a] and Hanash [b], Winstead and Irving; evidence of record). Clearly further research would be required to reasonably confirm the real world context of the asserted utility, i.e., whether the PRO1069 polypeptide or antibodies binding the polypeptide can serve as a reliable diagnostic marker for kidney tumors or as a therapeutic target for treatment of kidney tumors. Accordingly, the claimed utility is not substantial.

From pp. 7-11 of the response, Applicant refers to the first declaration of Mr. Grimaldi filed under 37 CFR 1.132 (filed 8/16/04) and argue against the Hu et al and LaBaer references and cites the art of Kuo et al. Further, it is asserted by Mr. Grimaldi that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Mr. Grimaldi also asserted that, if a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, i.e., to screen samples to differentiate between normal and tumor. It is further asserted that the PTO's assertions are contradicted by Mr. Grimaldi's statement, "[T]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (pg. 8) Applicants' assert that this declaration makes clear that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, how high the level of expression is in normal tissue is irrelevant. Further, applicants' argue that Mr. Grimaldi states that if a difference is detected using these techniques, "this indicates that gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes." (pg. 8). Thus, applicants' contend that it is the uncontested opinion of an expert in the field that the results are reliable enough to indicate that the claimed antibodies are useful as diagnostic tools. Applicant notes that an affidavit cannot be disregarded solely because it was signed by the applicant (citing MPEP 716.01(c)). This has been fully considered but is not found to be persuasive. The examiner acknowledges that the affidavit cannot

be solely disregarded because it was signed by the applicant. The MPEP makes clear, "factual evidence is preferable to opinion testimony..." The MPEP also makes clear, "opinion" testimony is entitled to be considered, i.e., it is "admissible" in an ex parte proceeding. MPEP 716.01(c) as cited by applicant. The mere fact that opinion testimony is admissible (i.e., it is entitled to be considered) does not per se mean it must be accorded controlling weight. Again, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a approximately 2-fold amplification of the message amplification (mRNA) (as suggested by the declaration) encoding PRO1069 is significant. However the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. It remains on this record that Hu et al analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease.

However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The specification fails to disclose any specific "fold amplification" that is required between normal and cancerous tissue for a diagnostic determination. Is a 1-fold, a 5-fold, a 10-fold, or a 100-fold difference required? If the "fold amplification" were disclosed in the specification to be 100-fold, for example, then the cDNA that encodes the PRO1069 polypeptide would likely have a specific and substantial utility as a diagnostic marker for normal kidney versus kidney tumors. However, such is not the case here. Most importantly, an assay using cDNA analysis as described in Example 18 merely measures the mRNA level; the chemical intermediate involved in translating DNA into protein and tracking this middle step reveals nothing about protein function, the abundance of protein in a cell, and modifications to proteins after they are produced – changes that may be critical in the development of diseases. Importantly, Example 18 does not measure the over-expression of the PRO1069 polypeptide of SEQ ID NO:50 or antibodies that bind to the polypeptide of SEQ ID NO:50. Regarding the interest of the expert in the outcome of the case, it is also noted that the expert has interest in the outcome of the case, since Mr. Grimaldi is listed as an inventor and is employed by the assignee.

Applicant again criticizes the publication of Hu et al and claims that the observations of Hu et al are due to the "bias in the literature" toward studying the most prominent targets. Further, Applicants' argue that Hu et al do not say that a correlation in their study means that genes with less than five-fold change in level of expression in

cancer cannot serve as a molecular marker of cancer. Applicants' arguments have been fully considered but are not found persuasive for the following reasons.

Hu et al teach that their study has two implications. First, a careful hunt for corroborating evidence of a role in breast cancer should precede any further study of genes with less than 5-fold expression level change. Second, any genes with 10-fold change or more are likely to be related to breast cancer and warrant attention (2nd paragraph of left column of page 412). Hu et al teach that it is likely that this threshold will change depending on the disease as well as the experiment (2nd paragraph of left column of page 412). Hu et al states clearly: "It is not uncommon to see expression changes in microarray experiments as small as 2-fold reported in the literature. Even when these expression changes are statistically significant, it is not always clear if they are biologically meaningful" (bottom of right column of page 411). Hu et al further states: "in any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study" (1st paragraph of left column of page 405). Further, it is reiterated that LaBaer teaches that reports of mRNA or protein changes of as little as two-fold are not uncommon and although changes of this magnitude may turn out to be important, most are attributable to disease-independent differences between samples. In view of the limited disclosure in the instant case, lack of disclosure of the "fold amplification" that was used to determine whether a higher expression, i.e., "more highly expressed" was significant, lack of the statistical analysis, and lack of establishment of a correlative link between gene expression and protein level or a causal link between mRNA expression

and kidney tumour, the teachings of Hu et al and LaBaer support the examiners position that further research is needed to reasonably identify or confirm a substantial utility for the instantly claimed polypeptide of SEQ ID NO:50 (PRO1069) and the antibodies binding the polypeptide. Further, it is curious that applicant argues with the first Grimaldi declaration as being relevant to the utility of the claimed invention, yet the cited art of Hu and LaBaer are irrelevant according to applicant. The Grimaldi declaration and the art of Hu and LaBaer are limited to gene expression and not polypeptide levels.

Regarding applicants remarks and the submission of Kuo et al, the "good correlation between mRNA and protein expression" was found after treatment with the potent immunostimulating agent CpG. It is not clear what effect, if any, CpG treatment will have on PRO1069 mRNA and polypeptide levels. Further, unlike the present application, Kuo et al actually analyzed mRNA and protein levels and performed functional assays. The instant application merely measures mRNA and presumes that PRO1069 polypeptide levels will track with the changes in PRO1069 mRNA, without providing any evidence of how PRO1069 polypeptide levels change in normal kidney compared to kidney tumor and does not disclose any biological activity or function for the PRO1069 polypeptide. The specification does not provide any evidence that the PRO1069 polypeptide can be used in a diagnostic or therapeutic setting, what information the PRO1069 polypeptide expression provides the clinician, such as the status of the cancer, or the direction in which therapy should proceed.

In response to the Examiner's argument in the previous office action, Applicants summarize the second portion of their argument as such: "it is well-established in the art

that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1069 polypeptide in kidney tumors, it is likely that the PRO1069 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools" (pg. 12). Applicants argue that the references cited in the rejection are not contrary to Applicants' asserted utility. The examiner acknowledges applicants remarks regarding the art of Hanna et al, however, applicant is relying on increased PRO1069 mRNA expression levels and not gene amplification as disclosed in Hanna et al. Thus, Hanna et al is not relevant to the present utility issue. Beginning at pg. 13 of the response applicant argues the art of Greenbaum et al, referencing Anderson and Sielhamer (Electrophoresis 1997: 18:533-537); Lichtinghagen et al (European Urology 2002; 42:398-406); Chen et al (Mol. And Cell. Proteomics 2002; 1:304-313) and Ornoft et al (Mol. Cell. Proteomics. 2002 1(1):37-45). Applicants' arguments with respect to the above references are similar for that of Haynes and Gygi. Applicant acknowledges the lack of correlation between mRNA levels and protein levels in the art, yet applicant argues that this is not contrary to their assertion that a change in mRNA level generally leads to a change in protein level and a change in protein without a change in mRNA is not contrary to Applicants' assertions. Applicants' arguments have been fully considered but are not found to be persuasive. While the lack of correlation between mRNA and protein is not dispositive that a change in mRNA generally leads to a change in protein level, it does not support applicants' assertion that such a correlation exists.

Applicant has not provided any facts or evidence that a correlation between a change in PRO1069 mRNA levels results in a corresponding change in PRO1069 polypeptide levels that is tumor-dependent, consistent and measurable.

With regard to the references of Haynes, Gygi, and Chen, Applicants argue that these studies only provide teachings regarding the predictability of the correspondence of steady-state mRNA and protein levels, and do not speak to whether or not a detectable change in mRNA level will lead to a detectable change in protein level, and therefore are not relevant to Applicants' argument (pg 15-18). The Examiner finds these arguments persuasive. The Examiner agrees with Applicant that these references do not provide teaching as to whether changes in mRNA expression are generally reflected as changes in protein expression.

Applicants further contend that the limited teachings in Chen that do address changes in mRNA level support corresponding changes in the level of encoded protein (pg 15). Specifically, Applicants argue that Figures 2A-2C show a correlation between mRNA/protein pairs for three specific genes, and that this supports Applicants' assertion of a correlation between mRNA and protein changes.

Applicant's arguments have been fully considered but are not found to be persuasive. The results in Chen shown in Figure 2A-2C represent three examples wherein protein levels were correlated with mRNA (out of 17 identified). Chen found 137 protein spots wherein protein levels were not correlated with mRNA levels. However, Chen does not report the individual variation within any of these samples (which included normal tissue and tumor tissue). Therefore, these samples may or may

not have included mRNA and/or protein levels that were differentially expressed. Chen simply does not provide enough information to address the issue whether changes in mRNA levels generally result in similar changes in protein levels. All that Chen clearly teaches is that mRNA levels do not predict protein levels, as they disclose at pg 304 that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue" (see pg 304, right column).

In contrast to Applicants' assertion that a changes in mRNA level generally leads to a change in protein level, Lian et al. (2001, Blood 98:513-524; IDS reference 79 filed 4/11/06) show a lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302; IDS reference 14 filed 10/14/05) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

Applicants also contend that the relevant art does teach a correlation between mRNA and encoded protein levels; in support of this argument Applicants submit Exhibits 17-24, containing a total of 33 references (pp.23-25).

Applicants' arguments have been fully considered but are not found persuasive. With the exception of Exhibit 17 (Futcher), Exhibits 17-24 are all directed to analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general. A more comprehensive analysis like Haynes (80 proteins examined), Gygi (150 proteins examined), Chen (164 proteins examined) or Futcher (148 identified proteins) more accurately describes general trends. The Examiner agrees with Applicants that Futcher is a study similar to Gygi but reaches different conclusions that Gygi. However, Futcher also teaches, "the correlation is far from perfect, there is at least a 10-fold range of protein abundance" (pg 7360) and "Despite generating broadly similar data, Gygi et al reached markedly different conclusions...Gygi et al feel that mRNA abundance is a poor predictor of protein abundance...These different conclusions are partly a matter of viewpoint. Gygi focuses on the fact that the correlations of mRNA and codon bias with protein abundance are far from perfect, while we focus on the fact that, considering the wide range of mRNA and protein abundance and the undoubted presence of other mechanisms affecting protein abundance, the correlations are good" (pg 7367 of Futcher, 1999. Molecular and Cellular Biology. 19(11): 7357-7368; Applicants only submitted the abstract of Futcher; the Examiner has placed the entire Futcher reference on the PTO-892 attached to this Office Action). For these reasons, the Examiner maintains that these references demonstrate the mRNA levels do not necessarily correspond to protein levels, although as noted above the Examiner acknowledges that these references do not address

whether observable changes in mRNA levels will be reflected as observable changes in protein levels.

With respect to Lichtinghagen and the Anderson and Seilhamer articles, Applicants' arguments are found persuasive that these references also do not address changes in mRNA levels, because the mRNAs studied by Lichtinghagen show either no change or little change (33%) in expression between normal and differential expression. It is noted that Applicants' argument with respect to Sterns and Wang reference (Exhibit 4) are addressed below.

Applicants refer to previously submitted declarations and references in support of their arguments that changes in the level of mRNA correspond to changes in the level of the encoded protein (pg. 19) and applicant refers to their remarks of record. This has been fully considered but is not found persuasive for reasons already of record. Applicants also assert that the references of Alberts [a], Alberts [b], Lewin, Zhigang, and Meric support the statements of Grimaldi and Polakis and applicant refers to their remarks already of record.

The following is reiterated for applicant's convenience. While the Examiner agrees with the teachings of Alberts [a], [b] and Lewin that initiation of transcription is the most common point for a cell to regulate the gene expression, it is not the only means of regulating gene expression. For example, Alberts [a], [b] and Lewin also teach that there are a number of other controls that can act later in the pathway from RNA to protein to modulate the amount of protein that is made, including translational control mechanisms and mRNA degradation control mechanisms. Furthermore, while

Zhigang provides an example of a high degree of correlation between protein and mRNA expression of a specific antigen, more comprehensive studies (Nagaraja (2006), Waghray (2001), and Sagynaliev (2005), cited below) show a different general trend. Applicants also have submitted Meric et al., 2002, which states the following:

> The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells. [M]ost efforts have concentrated on identifying differences in gene expression at the level or mRNA, which can be attributable to either DNA amplification or to differences in transcription.

Meric et al also goes on to state that gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability (see page 971, Introduction). Meric et al also teaches that there are a number of translation alterations encountered in cancer, including variations in the mRNA sequence as a result of mutations, alternate splicing and transcription start sites, alternate polyadenylation sites, and alterations in the components of the translation machinery (see pages 973-974).

In addition to the previously submitted references, Applicants submit 81 new references (Exhibits 4-15) in support of their argument. These references have been fully considered by the Examiner but are not found to be persuasive. First, except for the Orntoft reference, each of the references submitted by Applicants is directed to a single gene, or a small number of genes. These references are consistent with Chen who found 17% of proteins do show correlation between mRNA and protein, and the examples of these proteins in Chen that show that changes in mRNA correlate with changes in protein level. However, these studies examining the expression of small

numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined, specifically, Nagaraja (2006), Waghray (2001) and Sagynaliev (2005) which are described below.

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one.

Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft compared the mRNA and proteins levels of about 40 well-resolved and focused abundant proteins with known chromosomal locations (see pg 42). The instant specification does not teach whether or not PRO1069 is a "well focused abundant" protein with a known chromosomal location as characterized by Orntoft. Furthermore, other relevant publications (Nagaraja (2006), Waghray (2001), and Sagynaliev (2005)) report that increases in mRNA and protein samples are not correlated (see below).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a change in the mRNA level. Comprehensive studies comparing changes in expression of the transcriptome and proteome support this argument. Nagaraja (2006) teaches, "We have characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231)...the proteomic profiles indicated altered abundance of few proteins as

compared to transcript profiles" (See abstract of Nagaraja, 2006, Oncogene. 25: 2328-2338). Nagaraja further teaches, "The comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (pg 2329) and "As dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (pg 2335). Similarly, Waghray (2001) teaches, "we have analyzed gene expression changes induced by dihydrotestosterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels" (see Abstract of Waghray, 2001. Proteomics. 1: 1327-1338). Waghray identified transcripts from 16570 genes and found "351 genes were significantly altered by DHT treatment at the RNA level." Waghray identified 1031 proteins and found 44 protein spots that changed in intensity (either increased or decreased). Twenty-nine of these proteins were identified and "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level (Table 4)". If changes in protein generally reflected mRNA changes, based on the fact that 2% of the genes analyzed had a change in transcript levels (351 out of 16570 genes), one would expect at least 2% of protein levels to change, or 22 out of 1031 protein spots. Therefore, it is significant that while Waghray found 44 proteins that did change, very few of the identified ones had a similar change in mRNA expression.

In a review of gene expression in colorectal cancer (CRC), Sagynaliev (2005, Proteomics. 5:3066-3078) teaches, "One thousand two-hundred and forty genes have been reported to be dysregulated (up- and/or down-regulated) in human CRC,

representing about 5% of the 20000-25000 human genes" (pg 3067). Sagynaliev also teaches, "a total of 408 proteins were found to be differentially expressed in human CRC in at least one study" and importantly, "It is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support that changes in mRNA expression frequently do not result in changes in protein expression. Therefore, the Examiner maintains that Applicants' measurement of an increase of PRO1069 mRNA does not provide a substantial utility for the encoded protein, or an antibody to the protein.

In view of the totality of the evidence the skilled artisan would not reasonably presume that the PRO1069 polypeptide is "more highly expressed" in normal kidney compared to kidney tumor based on the disclosure regarding PRO1069 mRNA expression without actually testing for PRO1069 polypeptide expression. Further experimentation would be required to determine whether a change in PRO1069 mRNA or polypeptide expression is tumor-dependent, consistent and measurable as well as its significance, if any. The requirement for such testing to reasonably confirm the asserted utility indicates that the asserted utility is not substantial, i.e., it is not in currently available form. One skilled in the art would do further research to determine whether or not the PRO1069 protein was underexpressed in kidney tumors compared to normal kidney. Such further research requirements make it clear that the asserted

utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. M.P.E.P 2107 I states:

> A '"substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In view of the totality of the evidence, the rejection for lack of utility is proper and is maintained.

8. The rejection of claims 1-5 under 35 U.S.C. 112, first paragraph, is maintained. As discussed above, since the claimed invention is not supported by a substantial utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Priority

Applicant claims priority to five previous applications in the preliminary amendment of 09 September 2002. Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of '328 is identical to the instant disclosure. However, priority is not granted to USSN 09/380,137, PCT/US99/12252 and 60/088,740 since these applications do not disclose the quantitative PCR analysis of a cDNA library measuring mRNA expression (and not microarray analysis) upon which applicant relies for utility of the instantly claimed polypeptides. Therefore, the filing date for the purpose of art rejections is deemed to be 24 August 2000. Applicant is reminded that benefit to

a prior-filed application requires written description and enablement under the first paragraph of 35 U.S.C. 112.

9. The rejection of claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(a) as being anticipated by Lal et al (WO 00/00610, 1/6/2000, cited previously on PTO-892 mailed 4/15/2004) is maintained.

The response filed 4/11/06 argues with the previously submitted Declaration under 37 CFR 1.131 by Goddard et al filed 10/14/2005 to establish prior invention of the claimed subject matter prior to Lal's publication date, i.e., 1/6/00 as applied. The Declaration filed on 10/14/2005 under 37 CFR 1.131 has been considered but is ineffective to overcome the applied reference. The evidence submitted is insufficient to establish a conception of the invention or reduction to practice prior to the effective date of the Lal et al reference. 37 CFR 1.131(b) provides three ways in which an applicant can establish prior invention of the claimed subject matter. The showing of facts must be sufficient to show:

> (A) (actual) reduction to practice of the invention prior to the effective date of the reference; or
> (B) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice; or
> (C) conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to the filing date of the application (constructive reduction to practice). MPEP 715.07.

While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete disclosure to another.

Conception is more than a vague idea of how to solve a problem. The requisite means themselves and their interaction must also be comprehended. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). In the instant case, the Declaration states that an experiment performed on June 13, 2000, in which primers were used to determine the expression level of DNA59211 (SEQ ID NO:49 encoding the claimed polypeptide SEQ ID NO:50) in various tumor samples. There must be a contemporaneous recognition and appreciation of the invention for there to be conception. Silvestri v. Grant, 496 F.2d 593, 596, 181 USPQ 706, 708 (CCPA 1974). There is insufficient evidence of a recognition or appreciation of the claimed invention or a permanent idea of the complete and operable invention prior to the experiment performed on June 13, 2000. Bosies v. Benedict, 27 F.3d 539, 543, 30 USPQ2d 1862, 1865 (Fed. Cir. 1994). It would have been impossible to envisage the expression level of DNA59211 in normal kidney compared to kidney tumor prior to the experimental work on June 13, 2000. Subsequent testing or later recognition may not be used to show that a party had contemporaneous appreciation of the invention. See MPEP 715.07.

The evidence submitted is insufficient to establish a reduction to practice of the invention in this country or a NAFTA or WTO member country prior to the effective date of the Lal reference. The Declaration is limited to facts on the expression of DNA59211 (i.e., the DNA encoding the claimed polypeptide of SEQ ID NO:50) in various tumor samples. A probable utility does not establish a practical utility, which is established by actual testing or where the utility can be "foretold with certainty." Bindra v. Kelly, 206 USPQ 570, 575 (Bd. Pat. Inter. 1979) (Reduction to practice was not established for an

intermediate useful in the preparation of a second intermediate with a known utility in the preparation of a pharmaceutical. The record established there was a high degree of probability of a successful preparation because one skilled in the art may have been motivated, in the sense of 35 U.S.C. 103, to prepare the second intermediate from the first intermediate. However, a strong probability of utility is not sufficient to establish practical utility.). See MPEP 715.07 and 2138.04 to 2138.06.

Furthermore, as stated in the previous office action, the earlier application must meet the enablement requirement and must contain a written description of the subject matter under 35 U.S.C. 112, first paragraph. Again, USSN 09/380,137, PCT/US99/12252 and 60/088,740 do not disclose the quantitative PCR analysis measuring mRNA expression (e.g., Example 18) and thus, do not meet the written description requirement under the first paragraph of 35 U.S.C. 112.

For these reasons the rejection is maintained.

10. The rejection of claims 1-2 and 4-5 are rejected under 35 U.S.C. 102(e) as being anticipated by Walker et al (U.S. Patent 6,277,574 B1, 4/9/1999) is maintained.

The response argues as above that the previously submitted Declaration under 37 CFR 1.131 by Goddard et al filed 10/14/2005, which according to applicant establishes conception of the claimed invention prior to April 9, 1999 and diligence in reducing the invention to practice. Applicant concludes that Walker is not available as prior art. This has been fully considered but is not found persuasive. The examiner's remarks above for Lal et al apply here as well.

For these reasons the rejection is maintained.

11. The rejection of claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al (U.S. Patent 6,277,574 B1, 4/9/1999) in view of Queen et al (U.S. Patent 5,530,101, issued 6/96, cited previously on PTO-892 mailed 4/15/2004) is maintained.

Applicant argues as above for Walker, i.e., Applicants have demonstrated conception of the claimed invention prior to April 9, 1999 and diligence in reducing the invention to practice. Applicant concludes that Walker is not available as prior art. This has been fully considered but is not found persuasive. The examiner's remarks above for Lal et al apply here as well.

For these reasons the rejection is maintained.

New Grounds of Objections

12. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention, i.e., ANTIBODIES TO PRO1069, or similar title that is clearly indicative of the claimed invention.

Conclusions

13. No claim is allowed.

14. This is a continued examination of applicant's earlier Application. All claims are drawn to the same invention claimed in the earlier application and could have been

finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER